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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/370,358	08/09/1999	LARRY A. SKLAR	UNM-MC146-UT	7997

7590

11/18/2002

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EXAMINER

BRANNOCK, MICHAEL T

ART UNIT

PAPER NUMBER

1646

DATE MAILED: 11/18/2002

28

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.
09/370,358

Applicant(s)
Sklar et al.

Examiner
Michael Brannock, Ph.D

Art Unit
1646



— The MAILING DATE of this communication appears on the cover sheet with the correspondence address —

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Aug 25, 2002
- 2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 35 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-6, 8-48, 51, and 53-57 is/are pending in the application
- 4a) Of the above, claim(s) 14 and 18-47 is/are withdrawn from consideration
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6, 8-13, 15-17, 48, 51, and 53-57 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirements.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☒ The proposed drawing correction filed on Aug 21, 2002 is: a) ☒ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ 6) ☐ Other: _____

Art Unit: 1646

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/21/02 has been entered.

Status of Application: Claims and Amendments

2. Claims 1-6, 8-48, 51 and 53-57 are pending.
3. Applicant is notified that the amendments put forth in Paper 26, 9/4/02 have been entered in full.
4. Claims 14 and 18-47 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, as maintained in Paper 19, 8/28/01

Withdrawn Objections/Rejections:

5. The rejection of claims 48, 49, 51 under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No: 5583010, as set forth in item 7 of Paper 24, 6/5/02, is withdrawn in view of Applicant's amendments to the claims.

Art Unit: 1646

Maintained and New Rejections:

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. Claims 1, 6, 9-13, 15-17, 48, 50, 51, and 53-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 5583010 in view of U.S. Patent No: 5639603 as applied previously to claims 1, 6, 9-13, 15-17, 50, 52 and 53-57 in item 9 of Paper 24 and recast below in view of Applicant's amendments.

U.S. Patent No: 5583010 disclose methods for non-cellular display (e.g. purified recombinant receptor, col 19, L65) of a 7TM receptor (Growth hormone releasing hormone receptor GHRH-R) comprising incorporating an attachment scheme to the receptor (col 20, L1-3), solubilizing the receptor by lysing cell membranes containing the receptor (e.g. col 10, 124-29), presenting the receptor with in conjunction with a solid support (col 19 L65-col 20 L12), presenting one ligand to bind to the receptor, wherein said ligand is known to bind to the receptor (e.g. GHRH), and combining receptor and ligand to accomplish binding (col 19 L65-col 20 L12). Also, U.S. Patent No: 558310 state that "these assays can be linked to a reporter such as an antibody, biological chemical..., which will express a radioactive, chemical, calorimetric or

Art Unit: 1646

luminescent signal" see col 20 L4-7; thus one of ordinary skill in the art would understand from this teaching, and particularly from the term "luminescent signal", that it is meant the receptor ligand pairs can be sorted by fluorescence.

The claims also stipulate that the method of sorting be flow cytometry and that the solid support be bead substrates appropriate for flow cytometry. Additionally claims 54-57 require that the tag be an epitope tag, e.g. either an N or C-terminal, or internal epitope. One of ordinary skill in the art appreciates that at col 20, first paragraph, U.S. Patent No: 5639603 refers to such attachment means in the statement "Solid phase assays can involve receptor attached to a solid support either chemically or immunologically..."

Although U.S. Patent No: 5583010 appears to be silent with regard to flow cytometry, flow cytometry is a well known method of sorting fluorescently labeled receptor-ligand pairs. U.S. Patent No: 5639603 teaches the general applicability of flow cytometry to the sorting of isolated solubilized receptors and their bound ligands, wherein the solid supports are beads appropriate for flow cytometry and for library screening (see col 31, L40-54). Further, Patent No: 5639603 teaches that the receptor (e.g. col 31, L58) or the ligand (col 36, L35-38) be labeled with a fluorescently labeled marker.

Therefore, it would have been obvious to one of ordinary skill in the art, at the time the invention was made, and with reasonable expectation of success to use beads as the solid support and to separate the receptor-ligand pairs by flow cytometry as taught by U.S. Patent No: 5639603, when practicing the assay of soluble receptors attached to solid supports as taught by

Art Unit: 1646

U.S. Patent No: 5583010. The motivation to do so was provided by U.S. Patent No: 5639603 wherein it is taught that "by adopting cell sized solid supports or beads, one can use flow cytometry for high sensitivity receptor binding analysis and facile bead manipulation" (see col 31, L47-54).

Applicant argues that the methodology employed in the 5639603 patent (to Dower et al.) differs from that of instant claims. Each of Applicant's assertions are addressed below. Applicant argues that Dower solubilizes and binds a ligand library to a bead, whereas Claim 1 requires the solubilization and subsequent attachment via a tether of a receptor to a bead. This argument has been fully considered but not deemed persuasive. The 5583010 patent teaches the solubilization of GPCRs and the subsequent attachment to beads. The paragraphs beginning at line 27 of col 31 of Dower discuss the diversity of methodologies known as "florescence activated bead sorting" as they are well known in the art. While Dower is particularly interested in identifying ligands of a receptor, as pointed to by Applicant, the point of the discussion of paragraphs beginning at line 27 of col 31 is to provide a brief outline of the multitude of strategies available and well known to the artisan in the art of "florescence activated bead sorting". Additionally, as set forth previously, Dower contemplate an assay wherein a receptor is tethered to a bead and the ligand is labeled for analysis using FACS, see col 36, lines 35-41.

Applicant argues that the methodology of Dower does not allow for real-time analysis using flow cytometer because the method requires a wash step before flow cytometer. This argument has been fully considered but not deemed persuasive. The wash step contemplated by

Art Unit: 1646

Dower at line 60 col 31 is inherent to that particular application of the general method. If one were using the method of Dower to analyze the interaction between a receptor and its known ligand, as Applicant points out, then a wash step would obviously not be required. The purpose of the wash is to remove receptors that have non-specifically bound to incorrect ligands - such complexes would obviously not be present in the scenario proposed by Applicant. These facts apply equally whether or not the ligand is tethered (as taught by Dower beginning at line 27 of col 31) or the receptor is tethered (as claimed in claim 1 and as taught by Dower at col 36, lines 35-41). Thus, Applicant's arguments, as they rely on the fact that the instant claims stipulate that the receptor is tethered, are not persuasive. Further, the skilled artisan appreciates that the act of cell sorting with FACS constitutes an analysis of the receptor/ligand interaction in real-time.

Applicant further argues that Dower seeks to determine the identity of bound ligand, whereas in the assay of claim 1 it is a known receptor that is bound to the bead and it is the interaction with the bound receptor that is analyzed. This argument has been fully considered but not deemed persuasive. Both Dower (col 36, lines 35-41) and the 5583010 patent (col 19 L65-col 20 L12) teach the analysis of bound receptors.

8. Claims 2, 3-5 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 5583010, in view of U.S. Patent No: 5639603 as applied to claims 1, 6, 9-13, 15-17, 48, 50, 51, and 53-57 above, and in further view of Robeva, AS *et al.*, *Drug Development Research* 39(243-252)1996, for the reasons set forth previously in item 10 of Paper 24.

Art Unit: 1646

Claims 2, 3-5 and 8 stipulate that the tether or attachment means be a C-histidine or an N-histidine tag and that the bead be a Ni-silica bead and that the step of solubilizing the receptor comprise lysing the cell membranes. The use of histidine tags in the receptor art is old. Further, it is well known that Ni-silica beads are used with histidine tags. Robeva et al. disclose a method of displaying a 7TM receptor (Adenosine receptor) comprising incorporating an attachment scheme (e.g. hexahistidine tag) into the Adenosine receptor (GPCR construct), solubilizing the receptor by lysing membranes comprising the receptor (page 245), presenting the receptor on a solid support (e.g. Ni-NTA agarose, page 245), wherein said method further comprises the step of combining the receptor and a ligand to accomplish binding (see page 244, col 2).

Additionally, whether to use the tag at The N or C-terminal is an obvious matter of routine optimization of operating parameters. Further, Robeva teaches that the step of incorporating an attachment scheme comprises incorporating the tag (coding sequence) into an oligonucleotide: see page 244, MATERIALS AND METHODS, wherein the method of subcloning the Adenosine receptor is referenced in Robeva et al., 1996, Biochem. Pharm. 51:545-555, wherein it is indicated that the tags are incorporated using a 30 base pair oligonucleotide, see Robeva et al., 1996, Biochem. Pharm, page 554.

Therefore, it would have been obvious to one of ordinary skill in the art, at the time the invention was made to, with reasonable expectation of success to use histidine tags as taught by Robeva, as the attachment means for the assay disclosed by U.S. Patent No: 5583010 and modified according to the teachings of U.S. Patent No: 5639603, as discussed above. The

Art Unit: 1646

motivation to do so was provided by Robeva, AS et al., Drug Development Research wherein it is stated that their method should be useful for other proteins and for a variety of methods including reconstitution assays (see page 554), reconstitution assays being required for solubilization of the receptor, as per the instant invention.

Applicants arguments regarding the applicability of US Patent No: 5583010 and U.S. Patent No: 5639603 are addressed above.

Conclusion

No claims are allowable.

9. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR

Art Unit: 1646

1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Thursdays from 8:00 a.m. to 5:30 p.m. The examiner can also normally be reached on alternate Fridays.


If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

November 7, 2002


YVONNE EYLER, PH.D.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 160C